

## STAT3 ProGenotyper<sup>®</sup> Test

**Test Name:** STAT3 ProGenotyper<sup>®</sup> Test

**Alternative Names:** Hyper IgE Mutation Test (HIES)  
Job's Syndrome Mutation Test

**Test Code:** 3099

**CPT Code:** 83890, 83898 x 5, 83891 x 5, 83904 x 8,  
83912

**Clinical Utility:**

This test is intended to detect autosomal dominant STAT3 mutations associated with type 1 Hyper-IgE Syndrome (AD-HIES, also known as Job's Syndrome).

**Specimen Requirement:**

- 2mL whole blood (EDTA)
- Ship **overnight** at ambient temperature

**Background:**

AD-HIES or Job's Syndrome was first described in 1966 as hyperimmunoglobulinemia E characterized by recurrent staphylococcal abscesses, pneumonia, eczema, hyperextensibility, and extreme elevation of IgE levels. Mutations in STAT3 (signal transducer and activator of transcription 3) underlie the sporadic and dominant forms of hyper-IgE syndrome. STAT3 signaling is critical in the generation of Th17 cells, and IL-17 production by T-cells is absent in HIES individuals. These Th17 helper T-cells are believed to be critical in the clearance of fungal and extracellular bacterial infections. Normal keratinocytes and bronchial epithelial cells are deeply dependent on the synergistic action of Th17 and classical proinflammatory cytokines, thus recurrent staphylococcal infections confined to skin and lung in this syndrome are contrasted with more systemic infections in neutrophil-deficient patients.

**Units and Normal Reference Range:**

STAT3 exons 12-16, 20, and 21 are sequenced and compared to reference sequence NG\_007370. The great majority of mutations occur in these exons, in the DNA-binding domain, the SH2 domain, and the trans-activation domain. Dominant-negative mutations of STAT3 account for 95% of AD-HIES cases with a clinical score >40<sup>3</sup>. The remaining 5% of HIES patients without STAT3 mutations may have a mutation in an unidentified locus. STAT3 AD-HIES mutations often occur *de novo*. Results are reported as no mutation detected, heterozygous (HET) mutation (carriers), homozygous (HOMO) mutation, or unknown (UKN) mutation. A mutation that has not previously been reported in the literature is considered unknown.

**Method:**

1. Patient DNA is extracted from whole blood.
2. Regions of the STAT3 gene are amplified by PCR from the genomic DNA and the products of each fragment are purified.
3. Cycle sequencing is performed with one or two sequencing primers per STAT3 fragment.
4. These products are purified and run on the ABI3130 or 3730 Genetic Analyzer.
5. The resulting exons and exon/intron boundaries are compared to the reference sequence.

**References:**

1. de Beaucoudrey L, Puel A, Filipe-Santos O, et al. 2008. Mutations in STAT3 and IL12RB1 impair the development of human IL-17-producing T cells. *J Exp Med*. 205(7):1543-50.
2. Freeman AF, David J, Hsu AP, et al. 2010. Autosomal dominant Hyper IgE Syndrome. *Gene Reviews*, NIH. PMID 20301786.
3. Holland SM, DeLeo FR, Elloumi HZ, et al. 2007. STAT3 mutations in the hyper-IgE syndrome. *N Engl J Med*. 357(16):1608-19.
4. Milner JD, Brenchley JM, Laurence A, et al. 2008. Impaired T(H)17 cell differentiation in subjects with autosomal dominant hyper-IgE syndrome. *Nature* 452(7188):773-6.
5. Minegishi Y and Karasuyama H. 2009. Defects in Jak-STAT-mediated cytokine signals cause hyper-IgE syndrome: lessons from a primary immunodeficiency. *Int Immunol* 21:105-112.
6. Minegishi Y, Saito M, Nagasawa M, et al. 2009. Molecular explanation for the contradiction between systemic Th17 defect and localized bacterial infection in hyper-IgE syndrome. *J Exp Med*. 206(6):1291-301.
7. Pasic S, Stojkovic O, Metin A, Karasuyama H. 2007. Dominant-negative mutations in the DNA-binding domain of STAT3 cause hyper-IgE syndrome. *Nature* 448(7157):1058-62.
8. Paulson ML, Freeman AF, Holland SM. 2008. Hyper IgE syndrome: an update on clinical aspects and the role of signal transducer and activator of transcription 3. *Curr Opin Allergy Clin Immunol*. 8(6):527-33.
9. Renner ED, Rylaarsdam S, Añover-Sombke S, et al. 2008. Novel signal transducer and activator of transcription 3 (STAT3) mutations, reduced T<sub>H</sub>17 cell numbers, and variably defective STAT3 phosphorylation in hyper-IgE syndrome. *J Allergy Clin Immunol* 122:181-187.

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## Test Information Sheet

### STAT3 Gene Analysis for Hyper IgE Syndrome

**Also known as:** Hyper-IgE Recurrent Infection Syndrome; Job's Syndrome; HIES

**Mendelian Inheritance in Man Number:**

147060 Hyper-IgE Syndrome

102582 STAT3 (Signal Transducer and Activator of Transcription 3)

**Clinical features:**

Patients with autosomal dominant, STAT3-associated, Hyper-IgE Syndrome have lifelong eczema, usually from birth, and recurrent staphylococcal skin abscesses (recalling the infliction of the biblical character Job). The abscesses are “cold”, i.e. with remarkably little inflammatory response. Serum IgE levels are characteristically at least 10-fold elevated. Patients are prone to cyst-forming pneumonia (typically staph, hemophilus or pneumococcal) and mucocutaneous candidiasis. The face may be coarse and asymmetric. Non-traumatic fractures and scoliosis are typical, and dental deciduation is delayed. Other features reported include hyperextensibility, coronary artery aneurysms, brain lesions, craniosynostosis, and Chiari malformations.

**Inheritance pattern:** Autosomal dominant

**Reasons for referral:**

1. Confirmation of a clinical diagnosis
2. Genetic counseling
3. Prenatal diagnosis

**Test method:**

Analysis is performed by complete bi-directional sequencing of exons 12 –16, 20 and 21, where all mutations in the first 3 publications were found<sup>1,2,3</sup>. This is considered a “selected exons” or “hotspot” test. It examines amino acids 380-488 and 583-700. Mutations identified in the first person of a family to be tested are confirmed by repeat analysis using sequencing, restriction fragment analysis, or another appropriate method. If no mutation is found in the seven exons tested, analysis of the remainder of the 24 exons of the STAT3 gene is available upon request.

**Test sensitivity:**

STAT3 mutations are the predominant cause of Hyper-IgE Syndrome (HIES), and mutations strongly tend to occur in exons 10-16, 20 and 21. Sequence analysis of these exons is expected to detect at least 95% of STAT3 mutations.

**Mutation spectrum:**

The STAT3 mutations that occur in HIES patients all correspond to mutation types that are readily detected by sequencing. They are single amino acid deletions or substitutions, predominantly located in the DNA-binding domain (exons 10-16, of which exons 12-16 are studied) or SH2 domain (exons 20 and 21).

***Specimen Requirements and Shipping/Handling:***

- *Blood* - A single tube with 1-5 mL whole blood in EDTA. Ship overnight at ambient temperature, using a cool pack in hot weather. Specimens may be refrigerated for 7 days prior to shipping.
- *Buccal Brushes* - As an alternative, use a GeneDx buccal kits (others not accepted). Submit by mail. Buccal specimens are not accepted on children under 6 months of age.
- *Prenatal Diagnosis*: 10 mL amniotic fluid, 5 mg CVS, or 2 T25 flasks. Ship overnight at ambient temperature, using a cool pack in hot weather. Call to discuss requirements for parental blood. Keep backup cultures.

***Required Forms:***

Sample Submission (Requisition) Form – complete all pages  
Payment Options Form or Institutional Billing Instructions

***Prices and Turn-Around Time - Fees are subject to change without notice:***

Test #312: Mutation detection in selected exons in a new patient = \$890; Approximately 6-8 weeks

Test #9011: Testing of a relative for one known mutation\* = \$350; Approx. 2-3 weeks

Test #902: Prenatal diagnosis for a specific known mutation\* = \$2000; Approximately 2 weeks

\*Please see our website for CPT codes/prices for carrier and prenatal testing: <http://www.genedx.com>

***CPT codes for mutation detection in a new patient - All codes and units apply:***

83891 x 6	units = \$ 90
83898 x 12	units = \$ 300
83894 x 6	units = \$ 90
83904 x 12	units = \$ 310
83892 x 2	units = \$ 40
83912 x 2	units = \$ 60

TOTAL                      \$ 890

***Possible ICD9 Codes that may apply to some patients with this diagnosis:***

288.1 Job's syndrome or chronic granulomatous disease  
481 Pneumococcal pneumonia  
482.x Other pneumonia  
513.0 Abscess of lung  
680.x Boil

***References:***

1. Minegishi Y et al., Dominant-negative mutations in the DNA-binding domain of STAT3 cause hyper-IgE syndrome, *Nature* 448:1058-1062, 2007
2. Holland SM et al., STAT3 mutations in the Hyper-IgE syndrome, *NEJM* 357:1608-1619, 2007.
3. Renner ED et al., STAT3 mutation in the original patient with Job's syndrome, *NEJM* 357:1667-1668, 2007